REMARKS

Entry of the foregoing, reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

Claims 1-6, 13-17, and 20-38 are currently pending. Claims 1-6, 13-17 and 32-38 stand withdrawn. Claims 21 and 31 are amended herein to address a typographical error. Claims 28-29 are canceled herein without prejudice or disclaimer. Applicants reserve the right to file at least one continuation application directed to any subject matter canceled herein.

Specification

The Office objects to the specification, stating that SEQ ID NO:7 is to E.Coli, and SEQ ID NO:8 is to Arabidopsis. The specification is amended herein to address this, as confirmed in the sequence listing itself.

Objections To The Claims

Claims 21 and 31 are objected to because of the recitation "thaliania", which is not supported by the specification. This is a spelling error, and claims 21 and 31 are amended herein to recite "thaliana". Claims 28 and 29 stand objected to as duplicates of claims 26 and 27, as the Office states that transformation and transfection are both simply methods of inserting a nucleic acid into a cell. Without acquesing in the objection, claims 28-29 are canceled herein. Applicants request the objections to the claims be withdrawn.

Rejections Under 35 U.S.C. §112, first paragraph

Claims 20, 21 and 24-31 stand rejected under 35 U.S.C. § 112, first paragraph, as the description of representative species encompassed by the genus is purportedly not fully described. Applicants respectfully traverse.

The test for sufficiency of descriptive support in an application is whether the disclosure of the application relied upon reasonably conveys to the artisan that the inventor had possession at the time the invention was filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991).

Additionally, "[i]t is not necessary that the claimed subject matter be described in *ipsis verbis* to satisfy" the requirement. *Heymes v. Takaya,* 6 U.S.P.Q.2d 1448, 1452 (Bd. Pat. App. & Int. 1988). Nor does the statute require a working example to meet the requirements of § 112, first paragraph. *Id.*

The Office asserts that Applicants have not provided information in regard the structure/function relationships which would be broadly applicable to other peptide deformylases. Applicants can provide structure/ function information. Applicants can further provide sequence information from a number of other species, allowing the skilled artisan to identify site-specific residues and regions which are either essential, non-essential, or instrumental in the activity and specificity of plant peptide deformylase. Thus, Applicants provide the necessary level of guidance such that those skilled in the art would easily and readily recognize that they were in possession of the claimed invention.

For example, Applicants have performed studies that demonstrate complete resistance of transgenic plants expressing either of two peptide deformylase sequences to peptide deformylase inhibitors and submit (Appendix A, attached). Further, Applicants have characterized the biochemical properties and specificity of both *Arabidopsis* plant peptide deformylases (see Dirk et al. (2001). Eukaryotic peptide deformylases. Nuclear-encoded and chloroplast-targeted enzymes in Arabidopsis. *Plant Physiol* 127:97-107 and Dirk, L. M., M. A. Williams, and R. L. Houtz. 2002. Specificity of chloroplast-localized peptide deformylases as determined with peptide analogs of chloroplast-translated proteins. *Arch. Biochem.* Biophys. 406:135-141), and also localized and characterized the exact biochemical process in plants that is dependent on plant peptide deformylase activity, and responsible for the lethality of peptide deformylase inhibitors (see Cai-Xia Hou, Lynnette M. A. Dirk and Mark A. Williams. Inhibition of peptide deformylase in Nicotiana tabacum leads to decreased D1 protein accumulation, ultimately resulting in a reduction of photosystem II complexes. *Am. J.Bot.* 91, 1304-1311. 2004). Thus, Applicants submit that this further data shows the inventors had possession of the invention.

Claims 20, 21 and 24-31 stand rejected under 35 U.S.C. § 112, first paragraph, as the specification, while being enabling for polynucleotide encoding an enzyme of plant peptide deformylase, purportedly does not provide enablement for any polynucleotide encoding a plant peptide deformylase.

Applicants again note that they provide sequence information from a number of other species, allowing the skilled artisan to identify site-specific residues and regions which are essential, non-essential, or instrumental in the activity and specificity of plant peptide deformylase.

Further, page 6 of the outstanding Office Action, the Office the lists four examples as to how Applicants failed to provide sufficient support in the specification (A through D), Applicants respond to each, in the order used in the Office Action.

(A) The Office asserts that the specification does not establish regions of the protein structure which may be modified without affecting plant peptide deformylase activity. In response, Applicants note that they have significantly altered both the N-terminal and the C-terminal region of plant peptide deformylase during efforts to generate forms which would readily crystallize (please refer to Appendix B, attached hereto). These modifications include removal of the N-terminal region to Lys-65 and removal of the C-terminal region to Arg-264. The effect of these modifications was assessed relative to changes in the kinetic parameters of peptide deformylase as well as inhibitor sensitivity. Although these were alterations in the sequence of plant peptide deformylase, Applicant note that they had little effect on activity.

(B) The Office asserts that the specification fails to establish the general tolerance of plant peptide deformylase, with regard to modification and extent of such tolerance. In response, Applicants again note that while the peptide deformylase was altered as noted above, the activity was not greatly affected. Applicants further submit that based on conserved active-site protein motifs and studies on bacterial peptide deformylase aimed at identification of residues important in inhibitor binding, Applicants targeted the appropriately similar residues in plant peptide deformylase (please refer to Appendix C, attached hereto). These results demonstrate that mutations at K159 in plant peptide deformylase DEF2 either decrease activity about three fold (alanine substitution) or completely destabilize the protein (glutamate substitution). Further, substitution of E166 with an alanine in plant peptide deformylase DEF1 completely abolishes enzyme activity. Thus, Applicants have refined and narrowed the understanding of what regions and specific amino acids can tolerate modifications.

(C) The Office asserts that the specification fails to establish a rational and predictable scheme for modifying any plant peptide deformylase residues with an expectation of obtaining the desired biological function. In response, Applicants have discovered a crystal structure for plant peptide deformylase DEF2 (coordinates available) which clearly identify the relationship between plant peptide deformylase DEF2 sequence and structure. Applicants have identified a potential structural difference responsible for the specificity of DEF2 for the N-termini of the D1 polypeptide, a polypeptide encoded by chloroplast DNA, translated in the chloroplast, and essential to all plants. Thus, using the sequence and structural information, inhibitors can be designed to capitalize on the structural preference of DEF2 for the N-termini of the D1 polypeptide, and other DEF2's can be engineered to have resistance to such inhibitors.

(D) The Office asserts that the specification fails to establish which of the possible choices is likely to be successful. Applicants refer to the comments above for A through C. Further, Applicants have constructed a thorough phylogenetic analyses of the distribution of amino acid substitutions throughout the available collection of peptide deformylase sequences from all organisms (please see Appendix D, attached hereto). These results are presented as a comparison of both the number and percentage of substitutions found at any location within the sequence of peptide deformylase 1 & 2 from plants as well as *E. coli*. There are a number of residue changes which suggest selection pressure in the evolution of peptide deformylase specifically adapted to plants. Thus, these changes are indicative of specific sites where residue changes are likely to affect peptide deformylase activity and/or specificity without adversely affecting enzyme stability and are useful as targets for mutational changes.

In light of the above, Applicants request that these rejections be withdrawn.

Rejections Under 35 U.S.C. §103

Claims 20, 21 and 24-31 are rejected under 35 U.S.C. §103 (a) as being obvious over Braun et al. (*FEBS Lett.* Jan 25, 1993; 316(2): 128-32) ("Braun") in view of Chen et al. (*Biochemistry* Feb 15, 2000; 39(6): 1256-62) ("Chen").

The Offices asserts that the skilled artisan would have been motivated to isolate the gene for peptide deformylase from *Arabidopsis thaliana* by Braun, which describes the N-terminal residue of a mitochondrial-encoded protein (cytochrome *b*) from potato tubers. Applicants respectfully traverse.

For a *prima facie* case of obviousness, the following three requirements must be met. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine the reference with another reference. Second, the proposed modification must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. Third, the prior art reference must teach or suggest all the limitations of the claims. The teachings or suggestions, as well as the expectation of success, must come from the prior art and not from applicant's disclosure. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); *Amgen, Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991); and *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).

The Office cites to Braun as providing evidence and disclosure of peptide deformylase in the mitochondria of potato, and states "one of ordinary skill in the art would have been motivated to isolate a gene of plant peptide deformylase from *Arabidopsis thaliana*......." from the results disclosed in Braun. Applicants disagree, and submit that Braun motivates the skilled artisan not to pursue a gene for peptide deformylase in any plant, as not expectation of success is provided. Further, the state of the art was such that coupled with Braun and Chen, the skilled artisan would not have been motivated to arrive at the present invention.

First, a large body of evidence existed at the time of Braun arguing against the presence of peptide deformylase in any eukaryotic species, including mitochondria(see Meinnel, T. et al. Evidence that peptide deformylase and methionyl-tRNA(fMet) formyltransferase are encoded within the same operon in Escherichia coli. *J. Bacteriol.* 175:7737-7740; and Meinnel et al. 1993. Methionine as translation start signal: a review of the enzymes of the pathway in Escherichia coli. *Biochimie* 75:1061-1075).

For example an extensive examination of 1,764 eukaryotic proteins including those synthesized in the mitochondria (see Boissel, et al. *J. P., T. J. Kasper, S. C. Shah, J. I. Malone, and H. F. Bunn.* 1985. Amino-terminal processing of proteins: hemoglobin South Florida, a variant with retention of initiator methionine and N alpha-acetylation. *Proc. Natl. Acad. Sci. U.S A* 82:8448-8452) found that none of the mitochondria proteins were deformylated, confirming results from other studies (Feldman, et al. 1974. Mitochondrial biogenesis. Retention of terminal formylmethionine in membrane proteins and regulation of their synthesis *J Biol. Chem* 249:3702-3709 and Mannhaupt, et al. 1985. Cytochrome b, the var 1 protein, and subunits I and III of cytochrome c oxidase are synthesized without transient presequences in Saccharomyces cerevisiae. *Eur. J Biochem.* 150:435-439). Furthermore, peptide deformylase was known to be an exceptionally unstable enzyme (Mazel, et al. 1994. Genetic characterization of polypeptide deformylase, a distinctive enzyme of eubacterial translation. *EMBO J.* 13:914-923 and Meinnel et al. Evidence that peptide deformylase and methionyl-tRNA(fMet) formyltransferase are encoded within the same operon in Escherichia coli. *J. Bacteriol.* 175:7737-7740), a fact which prevented its characterization for nearly three decades, even from *E. coli.* Thus, the skilled artisan would not e motivated to attempt the present invention by what was known in the art.

Further, Applicants submit that the results presented in Braun are circumstantial, and are merely results for a single polypeptide. No efforts were made in Braun to detect peptide deformylase activity, amino acid or nucleotide sequences. Finally, there are other well-described N-terminal processing enzymes which could have generated the N-termini observed by Braun for cytochrome *b* from potato tuber mitochondria. It is well known in the art that eukaryotes possess an enzyme known as N-formylmethionine aminopeptidase which specifically removes N-formylmethionine residues from polypeptides (see Sherriff, et al. 1992. Isolation and purification of N-formylmethionine aminopeptidase from rat intestine. *Biochim.*

Biophys. Acta 1119:275-280) usually in conjunction with another deformylase (see Ackerman, et al. N-formyl-L-methionine deformylase activity in human leucocytes and platelets. *Biochem. J* 182:885-887; Aronson, et al. 1969. N-Formylmethionine deformylase from Euglena gracilis. *Biochem. Biophys. Res. Commun.* 34:311-314, and Broom, et al. 1989. Partial purification and characterization of a formylmethionine deformylase from rat small intestine. *Biochem. J* 257:51-56). Thus, Braun and Chen motivate the skilled artisan to pursue another enzyme, rather than peptide deformylase as in the claimed invention. Braun and Chen, taken with what was known at the art at the time, provide circumstantial evidence at best that the peptide deformylase enzyme exists, and certainly not to the extent shown in the present claims. These references, taken together, fail to provide the skilled artisan with motivation or expectation of success.

In light of the above, Applicants request that this rejection be withdrawn.

CONCLUSION

It is respectfully submitted that all rejections have been overcome by the above amendments. Thus, Notice of Allowance is respectfully requested.

In the event that there are any questions relating to this Amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (703) 836-6620 so that prosecution of the application may be expedited.

Respectfully submitted,

BUCHANAN INGERSOLL PC
(INCLUDING THE ATTORNEYS FROM BURNS DOANE SWECKER & MATHIS)

Date: March 20, 2006

By: ______________________
Deborah H. Yellin
Registration No. 45,904

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620